

REMARKS/ARGUMENTS

Claims 1 to 60 are pending in the application, and claims 1 to 21 and 40 to 49 have been withdrawn from consideration. No claims have been amended, cancelled, or added herein. Applicants respectfully request reconsideration in view of the following remarks.

Alleged Obviousness

Claims 22 to 39 and 50 to 60 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,959,090 (the "Guzaev patent"). Applicants respectfully traverse the rejection because the Office Action has failed to establish *prima facie* obviousness.

To establish *prima facie* obviousness, the PTO must satisfy three requirements. First, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). Second, the proposed modification or combination of the prior art must have had a reasonable expectation of success, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Finally, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

The Guzaev patent fails to teach or suggest every limitation of the present claims. For example, the patent does not suggest methods for preparing oligonucleotides to which at least one conjugate group is attached. While the Guzaev patent describes methods for preparing oligonucleotides to which a *phosphate group* is attached, it fails to teach or suggest methods for preparing oligonucleotides to which a *conjugate group* is attached. As understood by those skilled in the art, a phosphate group is not a conjugate group. Moreover, the present specification describes numerous conjugate groups, which are qualitatively distinct from phosphate groups, that can be attached to oligonucleotides using the methods defined by the claims. For example, the specification lists intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, and polyethers as exemplary conjugate groups that can be attached to oligonucleotides using the claimed methods. (See page 11, line 26 to page 13, line 26 of the specification as filed). Accordingly, the Guzaev patent does not teach or suggest methods for preparing oligonucleotides to which at least one group that those of skill in the art would understand to be a conjugate group is attached.

Furthermore, the Office Action has failed to provide any objective evidence of a suggestion or incentive that would have motivated those of ordinary skill in the art to modify the teachings of the Guzaev patent to arrive at the claimed subject matter. In fact, the Guzaev patent fails to teach or suggest that the described methods for preparing oligonucleotides to which a phosphate group is attached can be used to prepare oligonucleotides of the kind now claimed.

Although the Office Action asserts that the Guzaev patent describes a process for preparing substantially pure oligonucleotides having a phosphate group at the 5'-terminus, referring to column 3, line 8 to column 5, line 15 of the patent (Office Action dated February

DOCKET NO.: ISIS-4723
Application No.: 09/823,031
Office Action Dated: February 11, 2003

PATENT

11, 2003, page 3), those of ordinary skill in the art would not consider a phosphate group to be a conjugate group. The patent, therefore, fails to teach or suggest a process for preparing oligonucleotides to which a conjugate group is attached. To the extent that the Office Action considers the intermediates described in column 4 of the Guzaev patent to be oligonucleotides to which a conjugate group is attached, those of ordinary skill in the art understand that conjugate groups are to remain attached to an oligonucleotide and are not protecting groups that are removed during synthesis or preparation of the oligonucleotide. Accordingly, those skilled in the art would not consider the intermediates described in the Guzaev patent to be oligonucleotides to which a *conjugate group* is attached, but, rather, would consider the compounds to be intermediates containing protecting groups that are generated during the synthesis of a 5' phosphorylated oligonucleotide.

The Office Action has failed to establish *prima facie* obviousness, and Applicants, accordingly, respectfully request withdrawal of the rejection.

DOCKET NO.: ISIS-4723
Application No.: 09/823,031
Office Action Dated: February 11, 2003

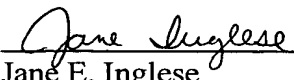
PATENT

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Respectfully submitted,

Date: April 29, 2003



Jane E. Inglese
Registration No. 48,444

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439